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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,571	03/29/2002	Paul Andrew Willis	06275-247US1	4502

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EXAMINER
MCKENZIE, THOMAS C

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,571	WILLIS ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-6 and 9* is/are allowed.

6)☒ Claim(s) *7,8 and 10-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to an application filed on 3/29/02. There are nineteen claims pending and nineteen under consideration. Claims 1-6, 8, 9, and 12 are compound claims. Claim 10 is a composition claim. Claims 13-19 are use claims. Claims 7 and 11 are method of synthesis claims. This is the first action on the merits. The application concerns some 2-amino-5-thio-thiazolo[4,5-d]pyrimidine compounds, compositions, and uses thereof.

Claim Objections

2. Objection is made to claim 12 under 37 CFR 1.75 as being a substantial duplicate of claim 1. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The phrase "for use in therapy" is a statement of intent. This is a purely mental act with no physical consequences. Thus, claim 12 is a compound claim with the same limitations as claim 1.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase in line 16, page 77 "X is a leaving group" is indefinite. What is the structure of this radical? In line 20, page 9, variable X is defined as "such as halogen". What other groups are included in this definition? As explained by A D McNaught & A Wilkinson, in "IUPAC Compendium of Chemical Terminology, 2nd Ed", "[t]he term [leaving group] has meaning only in relation to a specified reaction." This means that a universal list of such groups is not possible. The leaving groups in molecule (IIB) must differ from the leaving groups in other molecules such as the hydrogen atom in the nitration of benzene described in A D McNaught & A Wilkinson, in "IUPAC Compendium of Chemical Terminology, 2nd Ed".

The Examiner suggests claiming X is halogen.

4. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 13 provides for the use of a compound of formula (I), but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to

encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 13 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd. App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

5. Claims 14-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "a chemokine mediated disease" is indefinite. The passage spanning line 27, page 12 to line 10, page 14 provides a list of unrelated conditions using open language "examples of such conditions". What other diseases are contemplated? It is unclear what diseases and treatments applicant is intending to encompass. Determining whether a given disease responds or does not respond to such a receptor antagonist and thus, covered by the claim language, will require extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and

diseases Applicants intend to treat, the physician skilled in the clinical arts cannot determine the metes and bounds of the claim. Hence, the claims are indefinite.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for solvates of the claimed compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. There are two grounds for making this rejection. Firstly, what solvents are contemplated for making the "solvates"? What is the stoichiometery (empirical formula) of the claimed solvates?

Secondly, the numerous examples presented in the specification spanning pages 17-68 all failed to produce a solvate or hydrate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the

examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here: there is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly. It is unpredictable whether a particular solvent or water will form a solvate or hydrate with a particular host molecule.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims." *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Determining if any particular substrate would form a solvate would require synthesis of the substrate and subjecting it to recrystallization with a variety of solvents. This would be done at a variety of different temperatures and pressures because any particular hydrate or alcohol solvate is stable only over a limited range of conditions. The crystal formed would have to be characterized to determine if a hydrate or alcohol solvate had formed and what its composition was. This is a large degree of experimentation because of the unlimited number of

solvents that would have to be tested. b) There is no direction in the specification for producing solvates. 1) The lack of working examples was discussed above. d) The invention concerns chemical synthesis and chemical reactions.

e) The state of the art is summarized by David J. W. Grant (University of Minnesota--Twin Cities Campus College of Pharmacy, Annual Report) who writes, "Crystal Structures and Molecular Simulations Sulfonamides comprise a class of widely used antibacterial drugs. The crystal structures of various polymorphic phases have been solved and published. However, little work has focused on their solvates. In this laboratory, four sulfonamides (sulfapyridine, sulfadiazine, sulfamerazine, and sulfamethazine) were examined, and over a dozen solvates were discovered. The structures of these solvates are now being determined. The objectives of this study are to probe the intermolecular interactions between the drug and solvent in each solvate and to compare the crystal structures of the solvates with those of the parent drugs and among the solvates themselves. Ultimately, this group is gaining an understanding of how the solvent affects the properties of the drug and the reason behind the formation of each solvate. The researchers are working to predict solvate formation based on the structure of the drug." The sulfonamide drugs reported above are over fifty

years old. Yet in 1999 the synthesis of such solvates was not known even for such a well-studied class of molecules.

f) The artisan using Applicants' invention to make the solvates would be a process chemist or pilot plant operator with a BS degree in chemistry and several years of experience. g) The chemical arts, particularly those involving chemical reactions generally are understood to be unpredictable, *In re Marzocchi*, 169 USPQ 367, *In re Fisher*, 166 USPQ 18. The predictability in the art of making solvates is taught by West (Solid State Chemistry) as non-existent in 1988. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced.

In the first paragraph on page 365, West (Solid State Chemistry)says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host.

Thus, in the absence of any teaching in the specification of how to form any solvate of Applicants' compounds, undue experimentation will be required to prepare the claimed solvates.

7. Claims 14-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for treating human diseases. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection] have been summarized above. a) Determining if any particular claimed compound would treat any particular CXCR2-related disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different CXCR2-related diseases discussed above, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large degree of experimentation. b) The direction concerning treating CXCR2-related diseases is found in the passage spanning line 27, page 12 to line 10, page 14, which merely states Applicants' intention to do so. Applicants describe formulations in lines 16-24, page 15. Dosing methods required to practice their invention are described in the passage spanning line 34, page 15 to line 4, page 16. No specific dose or range of doses is recommended. Since no CXCR2-

antagonist has ever been used to treat any human disease, how is the skilled physician to know what dose to use for each of these different diseases? There are two *in vitro* assay described in the passage spanning line 15, page 68 to line 5, page 70 with no data but it is unclear if these IL-8 and GROα assays are correlated to human diseases. c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of disease, which involves physiological activity. e) The state of the clinical arts in CXCR2-related diseases is provided by Trivedi (Ann. Reports Med. Chem.) dated 2000, the third paragraph, page 193, "[t]he exact role of IL-8 in human disease is yet to be determined."

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the thousands of compounds of claim 1 as well as the hundred of diseases embraced by the term " CXCR2-related diseases". Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

8. Claim 17 is rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for preventing inflammation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants are not enabled for preventing any of these diseases. The only established prophylactics are vaccines not the 2-amino-5-thio-thiazolo[4,5-d]pyrimidine compounds such as present here. In addition, it is presumed that "prevention" of the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted.

Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of inflammatory diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent inflammation generally. That is, the skill is so low that no compound effective generally against inflammatory disorders has ever been found let alone one that can prevent such conditions.

The Examiner suggests removing the phrase "or at risk of,".

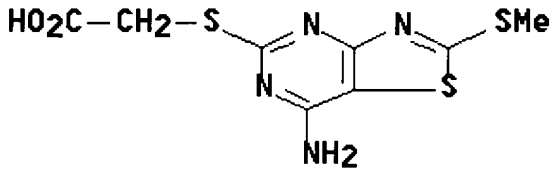
Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

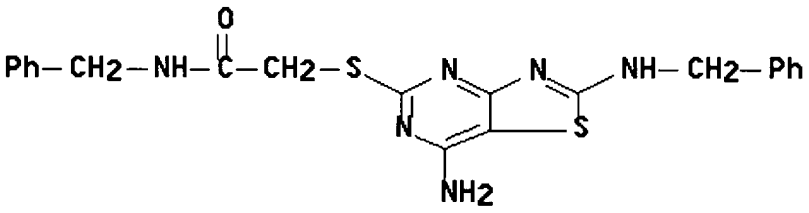
> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 8 is rejected under 35 U.S.C. 102(b) as being anticipated by Gewald (DE 4119767 A1). The compound shown below fits formula (IIB) with R^1 =methyl substituted by CO_2H, $R^2 = R^3$ = hydrogen, and X = the leaving group methylthio.

It has Registry Number 146381-65-9 and is found in Example 6, lines 45-52, page 3 of the reference.



10. Claim 8 is rejected under 35 U.S.C. 102(b) as being anticipated by Gewald (Journal fuer Praktische Chemie). The compound shown below fits formula (IIB) with R^1 =methyl substituted by $CONR^5R^6$, $R^2 = R^3 = R^6$ = hydrogen, R^5 = methyl substituted by phenyl, and X = the leaving group benzylamino. It has Registry Number 177356-01-3 and is found in the second formula, column 1, page 208 of the reference. It is called compound **17a** and synthesis is taught in the paragraph spanning pages 211-212.



Allowable Subject Matter

11. Claims 1-6, 9, and 10 are allowed. Claim 7 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in

this Office action and to include all of the limitations of the base claim and any intervening claims.

Conclusion

12. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Thomas C. McKenzie
Patent Examiner
Art Unit 1624

TCMcK
August 23, 2003